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Kinetic and isotope effect studies on the intermediacy of ethyl metathiophosphate in ethanolysis of O-ethyl N-1-adamantyl phosphoramidothioate

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Abstract

The fragmentation of O-ethyl N-1-adamantylphosphoramidothioate (**1a**) and its oxygen counterpart **1b** was examined in ethanol at 65–100 °C. The solvent hydrogen effect k_{EtOH}/k_{EtOD} and kinetic nitrogen effect k_{14}/k_{15} were determined at 80 °C. The rates and parameters of activation of ethanolysis of **1a** and **1b** are slightly different. The solvent effect k_{EtOH}/k_{EtOD} was found to be equal to 0.84 ± 0.05 for **1a** and 0.83 ± 0.04 for **1b**. The nitrogen effect k_{14}/k_{15} was found to be sensitive to replacement of sulfur by oxygen, and equal to 1.0083 ± 0.0004 for **1a** and 1.0065 ± 0.0006 for **1b**. The data indicate that proton transfer from the OH group to the amine moiety precedes the P–N bond breakage. The kinetic nitrogen isotope effect for the amine elimination recalculated for the pre-equilibrium step is equal to 1.0232 for **1a** and 1.0215 for **1b**. These results are consistent with the intermediacy of ethyl metathiophosphate in the solvolysis of **1a**.

Keywords: Metathiophosphate; Isotope effect; Deuterium; N-15

1. Introduction

Alkyl esters of phosphoramidic acids of type **1**, when substituted on nitrogen by large, sterically demanding groups, have recently been shown to undergo fragmentation in a unimolecular process that releases an alkyl metaphosphate as a transient intermediate [1–3]. When no trapping agent is present, the released metaphosphate immediately phosphorylates the unreacted phosphoramidic acid to form a pyrophosphate derivative (**3**). However, the metaphosphate may be intercepted by an added hydroxylic species, with the formation of a disubstituted phosphoric acid derivative. Both processes were demonstrated to follow first-order kinetics, as required by the mechanism of Scheme 1.

The requirement for steric bulk in the N-substituent is based on the repression of intermolecular condensation of the phosphoramidic acid, as well as bimolecular reaction of the phosphoramidic acid when an added hydroxylic species is present. Both processes require second-order kinetics, and lead to the same products as formed from the metaphosphate mechanism of Scheme 1. However, with the proper steric control, they can be discounted, as was easily demonstrated by the experimental determination of first-order kinetics. The elimination–addition mechanism of Scheme 1 was also supported by determination of the $^{14}N/^{15}N$ kinetic isotope effect (KIE) for the fragmentation of O-ethyl N-mesitylphosphoramidic acid. This is a highly useful technique for the detection of bond breakage in a transition state; it has, however, seldom been used in organophosphorus chemistry (for a recent use of k_{14}/k_{15} in phosphoryl transfer reactions see Ref. [4]), and to our knowledge the only application in elucidating the mechanism of a reaction where a P–N bond is involved is that described in our previous report [5]. The KIE value for the fragmentation of the phosphoramidic acid was 1.021,

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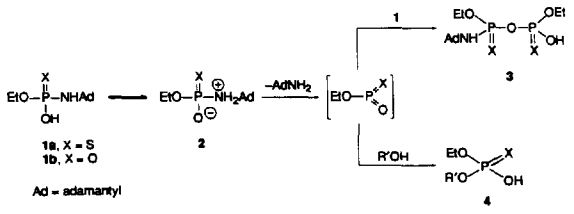

Scheme 1.

which was interpreted as consistent with the unimolecular fragmentation, as well as pointing to the dipolar form **2**, rather than the neutral form, as the species experiencing the fragmentation. The KIE value indicates that only breakage of the P–N bond occurs in the transition state; the transition state for the neutral form would additionally require cleavage of the O–H bond and formation of an N–H bond, and a KIE value near unity would be observed [6]. For the concerted mechanism, a normal (greater than unity) solvent hydrogen isotope effect should be observed.

In this paper, we address the question of the mechanism for the fragmentation of the sulfur counterpart of the phosphoramidic acids having structure **1**. O-Ethyl N-1-adamantylphosphoramidothioate (**1a**) has recently been synthesized, and found to undergo fragmentation with first-order kinetics in solutions of toluene in the presence of ethanol. The formation of ethyl metathiophosphate as a transient intermediate was therefore postulated [3]. Here we present the results of determination of the kinetics of the fragmentation of **1a** in ethanol or ethanol-*d* as solvent and trap. Similar kinetic data were obtained for the corresponding oxygen analogue **1b**, which permitted an analysis of the effect of a P=S group versus a P=O group in the fragmentation. The $^{14}N/^{15}N$ KIE value was also determined for both **1a** and **1b**. These studies give full support to the proposed metaphosphate elimination mechanism from the dipolar species **2**, formed in a pre-equilibrium transfer of a proton from oxygen to nitrogen.

2. Experimental

2.1. Materials

Substrates **1** and **2** were prepared according to methods described previously [1,3]. Ethanol (Pharmaco Products, Inc., anhydrous) and ethanol-*d* (Aldrich, 99.5 + % D) were used without purification. A solution of diazomethane in ether was prepared from Diazald (Aldrich).

2.2. Kinetic measurements

The rate of disappearance of substrate was determined from the diminution of its ^{31}P NMR signal, as described elsewhere [1,7]. Only signals of the substrate, product and standard (Ph_3PO) were detected.

The rate constants for 80 °C were calculated from the Arrhenius equation. The enthalpy and entropy of activation were calculated for 80 °C, according to Eyring theory. All data are given with standard deviations.

2.3. Isotope effects

The solvent hydrogen isotope effect was measured in independent kinetic runs. For determination of nitrogen KIE values, samples of 0.05 M ethanol solutions of **1a** or **1b** were sealed under argon in glass ampoules and kept at 80 °C. The reaction was quenched before completion by cooling at 0 °C; the solution was passed through a column of Amberlyst 15 (H^+) to remove the released 1-adamantylamine. To the amine-free solution, diazomethane in ether was added to convert the acids into methyl esters. The solvents were stripped off with a rotary evaporator and the methylated substrates (AdNH)(EtO)(MeX)P=O (**5**, X = S; **6**, X = O) were isolated by chromatography on silica gel plates (Aldrich) with 2-propanol–ethyl acetate (1:1) as the eluent ($R_f = 0.6$). The phosphoramidates were extracted from the silica with 2-propanol, and the alcohol was removed. Every sample contained at least 40 μmol of methylated substrate. The samples were combusted with a Heraeus elemental analyzer. The isotopic composition of nitrogen was measured with a Finnigan Delta S isotope-ratio mass spectrometer [8]. The relative isotopic ratios $\delta_f = (R_f/R_{st} - 1) \times 1000$ are given in Table 1. R_f is the isotopic ratio ($^{14}N^{15}N/^{14}N_2$) of the substrate after a fraction of reaction for the substrate, and R_{st} for standard N_2 from air.

Table 1
Kinetic nitrogen isotope effect for thermolysis of **1** and **2** in ethanol at 80 °C

Compound	Time (min)	f [a]	$\delta(f)$	k_{14}/k_{15}
1a	0	0	10.239	1.0083 ± 0.0004
			10.281	
	9	0.25	13.276	
	11.3	0.31	13.689	
	16	0.40	15.043	
	22	0.51	17.138	
	28	0.59	18.234	
	37	0.70	19.979	
1b	0	0	7.371	1.0065 ± 0.0006
	7.6	0.20	9.155	
	16.3	0.38	11.762	
	22.2	0.47	12.193	
	29.5	0.57	13.106	
	39.7	0.68	15.152	

[a] Value calculated from the rate constant.

The nitrogen kinetic isotope effect (Table 1) was calculated from the slope of the linear dependence:

$$\ln(1000 + \delta_f) = \left(\frac{1}{k_{14}/k_{15}} - 1\right)\ln(1 - f) + \ln(1000 + \delta_0)$$

where $y = \ln(1000 + \delta_f)$ and $x = \ln(1 - f)$.

2.4. Synthesis of O-ethyl S-methyl N-1-adamantylphosphoramidothioate (5) and O-ethyl O-methyl N-1-adamantylphosphoramidate (6)

A 0.3 g sample of **1a** was treated with an ethereal solution of excess diazomethane. Solvents were removed and the residue was crystallized from acetone ether/hexane to give **5**. Yield 0.16 g (51%), m.p. 106–106.5 °C. ^{31}P NMR ($CDCl_3$): δ 29.9. ^{1}H NMR ($CDCl_3$): δ 1.34 (t, 3H), 1.5–2.25 (m, 15H), 2.27 (d, $^3J_{PH}$ = 14.4 Hz, 3H), 2.78 (d, $^3J_{PH}$ = 8.4 Hz, 1H), 4.12 (m, 2H).

Anal. Found: C, 54.38; H, 8.24; N, 4.76. $C_{13}H_{24}NO_2PS$ Calc.: C, 53.96; H, 8.38; N, 4.84%.

The same procedure was applied to acid **1b** and gave **6** as a white solid, m.p. 86.5–87.5 °C (crystallized from ethyl acetate–hexane). ^{31}P NMR ($CDCl_3$): δ 8.3. ^{1}H NMR ($CDCl_3$): δ 1.33 (t, 3H), 1.45–2.25 (m, 15H), 2.47 (d, $^3J_{PH}$ = 8.4 Hz, 1H), 3.70 (d, $^3J_{PH}$ = 11.2 Hz, 3H), 4.07 (m, 3H).

Anal. Found: C, 57.38; H, 8.75; N, 4.8. $C_{13}H_{24}NO_3P$ Calc.: C, 57.13; H, 8.85; N, 5.12%.

3. Results and discussion

3.1. Reaction rate measurements

When thiophosphoramidic acid **1a** was thermally fragmented in ethanol, the only product was O,O-diethyl phosphorothionate (**4a**), readily recognized from its ^{31}P NMR shift of δ 55.9 [3]. The expected [1] first-order kinetics were observed; values for the rate constants at various temperatures are recorded in Table 2. From these data the usual thermodynamic parameters were calculated and are also given in Table 2. The oxygen counterpart **1b** was then subjected to the same measurements; kinetic and thermodynamic data are also recorded in Table 2.

The first-order rate constants for the two acids, **1a** and **1b**, are seen to be quite similar, but with a slightly higher value exhibited by the sulfur compound at 80 °C: **1a** $(5.37 \pm 0.19) \times 10^{-4}$ s^{-1}; **1b** $(4.83 \pm 0.19) \times 10^{-4}$ s^{-1}. The sulfur compound also has a slightly higher enthalpy of activation and smaller entropy of activation. The kinetic data are of great significance in that they support the proposed mechanism involving slow elimination of the metathiophosphate followed by fast addition of ethanol. Had the product been formed by direct displacement of the amino group in an S_N2 (P) process, the oxygen compound would have reacted much faster than the sulfur compound. Thus, trialkyl phosphanes hydrolyze about 30 times faster in basic

Table 2
Kinetics of the thermolysis of **1** and **2** in ethanol and ethanol-*d* at various temperatures

Compound/solvent	Temperature (°C)	Concentration (mol l^{-1})	Rate constant, 10^4k (s^{-1})	ln A (s^{-1})	E_a (kJ mol^{-1})	Rate constant at 353 K, 10^4k (s^{-1})	$\Delta H^{\ddagger}_{353}$ (kJ mol^{-1})	$\Delta S^{\ddagger}_{353}$ (J mol^{-1} K^{-1}) (e.u.)
1a/ethanol	65.4	0.048	1.38 ± 0.03	22.0 ± 1.1	86.7 ± 3.1	5.37 ± 0.19	83.8	−55.0 (−13.1)
	69.8	0.043	2.45 ± 0.09					
	80.3	0.048	5.73 ± 0.18					
	87.0	0.056	9.06 ± 0.13					
	99.3	0.048	24.93 ± 0.12					
1a/ethanol-*d*	65.4	0.051	1.86 ± 0.04	21.3 ± 1.5	84.0 ± 4.3	6.40 ± 0.32	81.0	−61.4 (−14.7)
	70.4	0.046	2.76 ± 0.12					
	80.3	0.049	6.71 ± 0.26					
	86.7	0.051	12.72 ± 0.49					
	100.2	0.048	27.09 ± 0.97					
1b/ethanol	64.9	0.047	1.38 ± 0.04	19.6 ± 1.2	79.9 ± 3.4	4.83 ± 0.19	77.0	−75.4 (−18.0)
	69.9	0.047	2.08 ± 0.11					
	80.0	0.102	5.48 ± 0.07					
	86.9	0.047	8.26 ± 0.13					
	99.3	0.051	18.62 ± 0.36					
1b/ethanol − *d*	65.1	0.048	1.84 ± 0.07	18.5 ± 0.80	76.3 ± 2.4	5.82 ± 0.16	73.3	−84.1 (−20.0)
	70.3	0.044	2.76 ± 0.09					
	80.7	0.043	5.94 ± 0.15					
	86.7	0.048	10.40 ± 0.50					
	100.2	0.047	22.76 ± 1.22					

media than the sulfur counterpart, necessarily following the S_N2 (P) pathway [9] (for P=O/P=S relative reactivity in aprotic solvents, see Ref. [10]). The rate effect is associated with the greater electronegativity of oxygen and the stabilization of the five-coordinate, negatively charged transition state. In contrast, monoalkyl phosphates, which are considered to fragment by metaphosphate elimination, are less reactive than the sulfur compounds [11]. Stereochemical data also support the intermediacy of the (planar) metathiophosphate [12]. Here the lower electronegativity of sulfur acts to stabilize the metathiophosphate and the transition state for its formation, because in the elimination–addition mechanism the charge on oxygen or sulfur diminishes. This stabilization effect of sulfur is well-known, and is responsible for the fact that salts of the trithiometaphosphate ion can be isolated [13], whereas the metaphosphate ion is known only in the gas phase [14]. Also relevant are the results of basic hydrolysis of phosphorodiamidates; it is believed that a three-coordinate metaphosphorimidate is formed in an elimination process, and the rates for the oxygen and sulfur compounds are essentially the same [15].

3.2. Kinetic isotope effect measurements

The approach used for KIE measurements has been described elsewhere [5]. The method involves the partial reaction of the phosphoramidic acids (**1a** and **1b**) with ethanol at 80 °C, and then the determination of the N^{14}/N^{15} ratio in the unreacted phosphoramidic acids. The residual acids, however, must first be stabilized by conversion to the methyl esters, using diazomethane for this purpose. In the case of the sulfur compound, methylation occurs not on the OH group but on sulfur [3], with the formation of ester (AdNH)(EtO)(MeS)P=O.

The fragmentation of acids **1a** and **1b** was also conducted in CH_3CH_2OD as solvent, where it can be assumed that almost complete exchange of the proton of the acids with deuterium has occurred [16]. The rate constants were greater in ethanol-*d*; the solvent hydrogen isotope effect k_{EtOH}/k_{EtOD} was found to be 0.84 ± 0.05 for **1a** and 0.83 ± 0.04 for **1b**. This is the reverse of the effect that would be expected if hydrogen is transferred from O to N in the transition state [6]. The lack of participation of a primary hydrogen isotope effect ($k_H/k_D > 1$) in the solvent isotope effect is, however, consistent with the view that the hydrogen transfer precedes the formation of the transition state for the fragmentation [17], as is depicted by the mechanism proposed in Scheme 1.

The methyl esters were purified on chromatographic plates and isolated for combustion to N_2 and determination of the ratio of N isotopes with an isotope-ratio mass spectrometer. The relative isotopic ratios δ_f are given in Table 1. The nitrogen kinetic isotope effects were calculated as described in Section 2, and are recorded in Table 1. The observed KIE values (k_{14}/k_{15}) were 1.0083 ± 0.0004 for acid **1a** and 1.0065 ± 0.0006 for acid **1b**. However, the observed KIE must be corrected to include a term for the pre-equilibrium transfer of proton from O to N. As discussed in our previous paper [5], the equation below applies, where K_{14}/K_{15} is an equilibrium isotope effect for the proton exchange and is estimated to be about 0.985 [18].

$$k_{14}/k_{15} = (k_{14}/k_{15})_{obs}/(K_{14}/K_{15})$$

The corrected KIE value for **1a** is therefore 1.0232, and for **1b** 1.0215. A similarly large KIE value (1.021) was found for the thermolysis of O-ethyl N-mesitylphosphoramidic acid [4].

Theoretical calculations for nitrogen leaving groups have shown that the magnitude of the KIE increases linearly with the fraction of bond cleavage [19]. The slightly higher KIE value for the sulfur compound may indicate more advanced P–N bond cleavage in the transition state than in that for the oxygen compound. This is consistent with the concept that metathiophosphate is more stable than the metaphosphate. In any case, the magnitudes of the KIE values for acids **1a** and **1b** are fully consistent with a mechanism involving cleavage of the P–N bond in the rate-controlling step, as depicted in Scheme 1.

4. Conclusions

The mechanism of ethanolysis of O-ethyl N-1-adamantylphosphoramidothioate **1a** and its oxygen counterpart **1b** was examined by kinetic and kinetic isotope effect measurements. **1a** fragments slightly faster (with slightly larger enthalpy of activation and smaller entropy of activation) than **1b**. The solvent hydrogen isotope effect is inverse, and the same for **1a** and **1b**. The kinetic nitrogen isotope effect was found to be sensitive to replacement of sulfur by oxygen, and indicates more advanced P–N breakage in a transition state, leading to formation of ethyl metathiophosphate. All data are consistent with an elimination–addition mechanism which involves a pre-equilibrium with proton transfer from the OH group to the amine moiety followed by P–N bond breakage.

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